Exhibit F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 1/PROLIFT, PROLIFT+M AND PROSIMA CASES**	**Master File 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF ELAINE DUNCAN, MSME, RAC

SCOPE:

I have been asked to address the developmental history, design control and risk management processes of Ethicon, Inc., Ethicon Women's Heath and Urology, a Division of Ethicon, Inc., Gynecare, and Johnson & Johnson (collectively referred to as Ethicon) associated with the design, development and risk management of Prolene Soft Mesh, Gynemesh PS, Prolift, Prolift+M and Prosima. I have also been asked to review and evaluate the report and opinions of Russell Dunn. The primary focus of this report is on Prolene Soft Mesh as a medical implant device and as a component of Gynemesh PS, Prolift, Prolift+M and Prosima.[1] My opinions are offered to a reasonable degree of professional certainty within my field of expertise and based upon my experience with medical device technology and regulation.

I have made an extensive review of documentation and testimonies, which are either specifically cited in this report or identified in Exhibit A.

BACKGROUND, EXPERIENCE AND QUALIFICATIONS

In 1987 I founded Paladin Medical, Inc., a consulting company dedicated to the service of medical device manufacturers and developers to ensure that start-up projects and new development companies would have the benefit of an executive-level regulatory and quality

[1] In this report I will refer to Prolene Soft Mesh, Gynemesh PS, Prolift, Prolift+M and Prosima collectively as "Prolene Soft Mesh Products." I am aware that Prolift+M contains an absorbable component along with the Prolene mesh component.

assurance professional. Today the company specializes in new medical technology development and regulatory strategies.

My training in medical devices began at the University of Kentucky. I graduated from University of Kentucky in 1974 with a Bachelor of Science Degree in Mechanical Engineering, with emphasis in biomedical engineering course work and collaboration with university physicians. 3M Medical Products Division recruited me directly from UK to conduct new product development at the new surgical products division. I was immediately assigned to conduct due diligence for an acquisition of a silicone rubber implantable neurological shunt, the first acquisition of an implantable product by the company. After the comparative product assessment, I was responsible for integration of the product into the 3M quality system, designed a new sterile package for the implant, and helped the new acquisition become compliant with the nascent Good Manufacturing Practices taking effect in 1976. For nine years I was either developing patentable medical devices of my own design, or ushering in other new acquisition implants, including implantable intraocular lenses and cardiopulmonary support technology. By 1981 I had completed the coursework for a doctorate in biomedical engineering and had been awarded a Masters' Degree in Mechanical Engineering – biomedical major from the University of Minnesota, while continuing to work full-time at 3M.

In 1982, after the first human implant of the Jarvik-7 artificial heart, I set aside my academic goals when I was recruited to the start-up company evolving from the University of Utah. As the Director of Regulatory Affairs and Quality Assurance, I shepherded the new company through the FDA review prior to receiving permission for the second human case. I conducted and reported to the FDA the failure analysis of the Shiley mechanical heart valve, which caused premature removal and replacement of half of the artificial heart in the first patient only days after implant. This investigation was critical to convincing the FDA to permit the second case. I was responsible for coordinating the training curriculum program involving calf-implant surgery for the cardiovascular surgeons who would qualify for the next artificial heart implant centers. I also submitted and managed the investigational device exemption (IDE) for one of the country's first cochlear implants that was licensed to the company.

After we successfully took the artificial heart company public, I decided to return to the Twin Cities. My heart valve investigation work brought me to the attention of the "Dingell Committee," which was investigating deaths caused by failure of the Shiley Heart Valve. Although the Safe Medical Devices Act (SMDA) had passed in 1990, the Subcommittee on Oversight and Investigation of the Committee on Energy and Commerce of the House of Representatives was clearly dissatisfied by the FDA's failure to resolve the problem. I served as a consultant to the Special Assistant to the Chairman, Rep. John D. Dingell of Michigan and contributed expertise to the report entitled *FDA's Failures in Medical Device Regulation and Corporate Breach of FDA's Honor System*, published for the One Hundred 1st Congress, Second Session, February 26, 1990. Through the next few years I continued as a liaison and consultant to the Chairman's Special Assistant and the publication of the report: *Less than the Sum of its Parts: Reforms Needed in the Organization, Management, and Resources of the Food and Drug Administration's Center for Devices and Radiological Health.* By introducing committee staffers to local medical device industry leaders through the Medical Alley organization, the committee was able to hear firsthand how improvements to regulations and practices at FDA could benefit patients and the medical device industry. Many of the reforms we recommended

were implemented in subsequent regulations and guidance documents by FDA. In fact, this set off a wave of FDA and congressional delegations coming to the Twin Cities for input into the regulatory system. Regulations that were finally issued in 1996 to move from the old "good manufacturing practices" to the current Quality Systems Regulation were a direct output of that and the many interactions between the FDA and "Medical Alley" leadership.

In 1984 I was recruited to join a start-up company developing a unique, synthetic coronary artery bypass graft in collaboration with the University of Minnesota. Under my leadership of the development and quality team we established sufficient fluid mechanics performance evidence of the venturi-graft to attract support from large medical device firms and biomaterial suppliers. I planned subsequent animal and clinical trials, which led to a Humanitarian Device Exemption. When I left the company as vice-president of new ventures, the small medical device firm was well on its way with three cardiovascular product lines.

I have held a certification as a Regulatory Affairs Professional (RAC) continuously since 1994. I am a member of numerous professional associations, such as the Regulatory Affairs Professional Society, American Association of Medical Instrumentation (AAMI), and American Society of Materials Testing (ASTM)-F4 Committee. I have been an active member of LifeSciences Alley (previously-Medical Alley), including a training contributor and chair of the regulatory special interest groups.

I served for more than two decades in numerous leadership positions in the Society For Biomaterials (SFB) and continue to be involved as a contributing member to various committees. I edited and produced "***Biomaterials Forum***" for nearly a decade and sponsored workshops on Design Control and Risk Analysis Workshops. I was co-chair and chair of various specialty meetings sponsored by the Society, including a three-part series on implant retrieval and implant histology, and a symposium at the Society and World Biomaterials conventions. In addition to my service to the Society for Biomaterials, I have frequently presented to medical device training and exhibition programs around the country. I have also contributed to the trade magazine published by CANON Communications, Inc. CA. I have authored various publications in the industry press and book chapters. (See curriculum vitae for details.)

I was awarded the C. William Hall Service to the Society For Biomaterials Award in 1999 and was subsequently nominated to the Office of President. Additional recognitions include the Medical Alley Award for Outstanding Contribution to the Heath Care Industry in 1992. In 2000, I was named to the University of Kentucky Engineering Hall of Distinction and served on the Dean's Advisory Committee to the UK College of Engineering and as an advisor to the Department of Biomedical Engineering.

As the Principal of Paladin Medical, I have consulted with more than 300 client companies, including three major global medical device manufacturers, as a special projects contractor. I have provided countless hours of pro bono consulting to start-up companies, university biomedical device engineers and physicians with an idea. I have filed or supported premarket notifications [510(k)], premarket approvals [PMA], investigational device exemptions [IDE] and Device Master Files [MAF] with the US FDA and organized Design Dossier and Technical Files for CE Mark. My clients span the globe from Austria to Australia. Through these endeavors and various professional organizations, I have provided quality assurance training to employees at

numerous companies, spearheaded failure mode and effects analysis and risk assessment programs, helped to establish numerous design history files, quality manuals and quality system procedures compliant with both 21 CFR 820 Quality Systems Regulations and the comparable ISO systems (now ISO 13485:2012.); including establishment of complaint procedures and programs to support Medical Device Reporting (MDR) and Vigilance Reporting in numerous firms. I am proficient in application of ever evolving international standards to U.S. marketed devices.

I have considerable experience with software and electronic medical devices but my specialty is implantable medical devices. I have been involved with "active implantable devices," such as defibrillators and long-term biomaterial-intensive medical products, some of which integrate with human tissues and bone. For example, I have successfully applied for 510(k)s to the US FDA for surgical mesh products for companies other than Ethicon. For one such firm I worked with FDA to satisfy the needs for the FDA's 522-order for post-market surveillance. I am therefore well versed in the quality, risk assessment and validation for surgical mesh devices for various applications.

SUMMARY OF AFFIRMATIVE OPINIONS

I will explain in detail my opinions below. The following is an overview of my affirmative opinions:

- In the design and development of its Prolene Soft Mesh Products, Ethicon met or exceeded all applicable industry standards intended to ensure that the devices are safe and performed to customer requirements.

- Ethicon conducted proper and thorough risk analyses in connection with the development of its Prolene Soft Mesh Products.

- Ethicon's Prolene Soft Mesh Products quality documentation, including but not limited to design history files, technical files and risk management documentation demonstrate thorough compliance with requirements for safety and performance.

- Independent regulatory assessments confirm that Ethicon fully complied with applicable standards designed to ensure safety and efficacy of its Prolene Soft Mesh Products.

SUMMARY OF REBUTTAL TO RUSSELL DUNN

An overview of my opinions in rebuttal to Dr. Dunn is stated as follows:

- Dr. Dunn has not provided any justification for his unfounded allegations against Ethicon's quality system; and in fact, the documentation from three generations of product development shows the dedicated effort by Ethicon to meet national and international standards and customer requirements.

- Dr. Dunn's opinion that Ethicon failed to provide feedback is wrong.

- All of Dr. Dunn's opinions concerning the design of Ethicon's Prolene Soft Mesh Products are wrong for each of the following independent reasons:

    a. he has failed to associate oxidative degradation with failure of an Ethicon Prolene Soft Mesh product to meet any design requirement such as failure to perform as a sufficient tissue bridge;

    b. he has failed to identify any clinical "harm" attributable to oxidative degradation of Ethicon's Prolene Soft Mesh Products.

- Proper risk analysis techniques would not consider oxidative degradation as a hazard for Prolene Soft Mesh Products implanted in the human body because there is no identifiable harm.

- Following proper Failure Modes Effect Analysis methods, medical industry practices and standards, plus information known from the company's internal reports, none of the reported clinical failure modes of the Prolene Soft Mesh Products would have reasonably caused Ethicon to further investigate, or test for, oxidative degradation.

- Dr. Dunn's opinions that Ethicon should have performed more testing are contrary to industry standards that urge not to sacrifice animals for unnecessary tests. In fact, Dr. Dunn's opinions that Ethicon should have performed more degradation studies conflict with the U.S. industry standard that requires that the FDA's CDRH Division be the decision-maker as to whether additional degradation studies are needed.

- Dr. Dunn's discussion and opinions concerning Ethicon's internal studies fail to consider the full context of the reports by selectively quoting only the portions that he believes fit his opinions. The fuller context of the internal studies reflect the cutting edge and balanced investigations conducted by Ethicon three decades ago.

- Dr. Dunn's opinions to the effect that Ethicon's internal studies indicate a need for additional studies are wrong because the report findings did not identify any adverse effect associated with the fulfillment of the essential purpose of the mesh: a tissue bridge. Dr. Dunn's opinion that external consultants "reported that oxidative degradation was a likely cause of polymer failure in its mesh devices in 2011" is a gross mischaracterization of the report.

- Dr. Dunn's opinions that oxidative degradation of Prolene mesh is a design defect are wrong because he is unable to identify how the effects of oxidation result in any mesh failure to perform as a tissue bridge (i.e., reinforcement).

HOW MEDICAL DEVICES ARE DEVELOPED TODAY

Most ideas for a medical product derive from a physician's experience. The idea may also be born from improvements and extensions of existing technology. Typically, two or more people begin to describe product expectations, which will become design or engineering "inputs." Where there is a clear unmet need or market demand, the product emerges from the concept stage. This is not a fixed bright-line in all cases, but when commitments begin we try to establish a consensus of product description and intended use.

The feasibility stage often involves prototypes using methods and materials at hand to demonstrate that the concept can take form. Typically, more inputs are sought, a basic understanding of technology requirements evolves, and the design is further refined. Often only rudimentary testing is feasible at this time. But at the end of this stage there should be a general understanding and agreement (written) that expresses the product's intended use and an understanding of how the product fits within the marketplace. Typically at this point there is some understanding of what risks and benefits – on a general level – may be attributed to the product. A formal design review will generally capture the decision to move to development and begin to capture design development documentation.

Development stages may have several sub stages depending upon the nature of the product. For example, an implantable product might be evaluated first in an animal model and perhaps later in a clinical trial. Development stages are captured in a Design and Development Plan. The initial plan is comprehensive, but by necessity evolves and is modified as new information is gained. Although dates and resources may be mapped, the key purpose of the Design and Development Plan is to define responsibilities for implementing the plan and ensuring clear descriptions of groups and activities required for the specific development process. As an example, groups may work on materials, sterile packaging, supporting instruments, electronics, or interface with other products. The project leader keeps these groups in focus by various key review meetings at milestone intervals or deliverables to test regimes.

Depending upon the development plan and the company's procedures, this is the time to refine "input requirements." As described above, physicians and users are major contributors to "inputs," but companies know that two additional major contributors to "inputs" cannot be ignored. First, 21 CFR Part 820 requires additional inputs to the performance and safety of medical devices. The US FDA may have also issued a guidance document on the technology or specific product which must be factored into the product design and testing plans. In fact, the guidance document may even list specific standards to which the product should adhere. Second, in some instances the FDA recognizes certain standards published by International or US standards organizations that are listed on the FDA website. Although the FDA may recognize a standard, it is not uncommon for the FDA to abridge the standard for review of premarket submissions, or refuse to recognize certain standards. See the FDA's *Guidance for Industry and FDA Staff Recognition and Use of Consensus Standards* issued on: September 17, 2007.[2] This document supersedes the "Recognition and Use of Consensus Standards; Guidance

[2] http://www.fda.gov/RegulatoryInformation/Guidances/ucm077274.htm (last accessed February 24, 2016).

for Industry and for FDA Staff" document issued on June 20, 2001. (Note discussion below explaining that the FDA has recognized ISO 14971:2007 but has not recognized ISO 13485.)

In addition to finalization of the input requirements, hazard analysis and risk assessments at various levels (design, process, user, software, hardware – if applicable) an overall risk management scheme is refined. The risk management plan incorporates how quality assurance functions will perform through the lifecycle of the product, into production and beyond. The quality and risk management plan includes the requirements for verification (usually specific physical testing against product requirements) and validation (assurance that the product meets the broader user needs, which may not always be reflected in the dimensions and physical attributes.) As with prior phases, development deliverables and reviews may be iterative. See ISO 14971:2007.

The design team analyzes the potential hazards that may occur should the product fail to meet the user (input) requirements. Thus, the team must analyze how the product may fail to achieve the requirement, and if that hazard has a potential to do harm, and the severity of the harm, should the hazard occur. And, part of the assessment is to understand how likely this potential may be. According to ISO 14971:2007, the concept of *risk* combines two variables: the probability of harm and the severity of harm. (Most failure mode and effects analysis programs also include the variable of "detectability" to help to focus on the opportunity for mitigation of the risk.)

The hazard analysis and risk assessment process is thorough and may be iterative as testing and mitigation measures affect the team's understanding of the potential to do harm and as the product moves through its various levels of evaluation. As mitigation programs take shape, the design level risk analysis is typically reviewed again to ensure that risks have been properly addressed. Sometimes risk mitigation, such as biocompatibility testing to ISO 10993, requires that the device, components, and materials are submitted to certified testing laboratories for independent assays. Products are often demonstrated to expert panels and focus groups for feedback. Increasingly the ultimate validation of the performance of a new product is the conduct of clinical trials. Monitoring clinical studies and reporting results is a highly regulated process and can take many years. Throughout the clinical trial process, the regulatory body for the country in which the study is conducted has oversight of the device and clinical outcomes.

Through intensive design meetings and reviews, the team determines that outputs meet inputs and that the risks that can be mitigated are managed. Beyond design changes, mitigations can take various forms, including training of the user, labeling, and limiting the intended use. Throughout the entire project the team documents decisions and testing. Members of the team work to refine user instructions, packaging and stability data. Information the customer or user will need evolves with the understanding of the device performance.

If future design changes are required, future development teams may need to return to the development records, which (per 21 CFR 820.30j) are maintained in the Design History File. (Note: ISO 13485 does not refer to, describe, or require a Design History File, and thus "13485-based" quality systems may overlook actively compiling the necessary design history documents required by FDA.) Often design review minutes, protocols, and reports play key roles in whether or not to institute a change to a product and how to validate the change. When a change could

alter an approved specification or input requirement, the team must be careful to determine how the change might affect risks, such as introducing new, unanticipated risks.

To increase efficiency of material and process validation, companies frequently refer back to materials and processes previously qualified if the analysis shows these were functional and safe. For example, Gynemesh PS, Prolift and Prosima use the Prolene Soft Mesh material. This reduces risk and improves probability estimates.

Biocompatibility is such an important part of the risk assessment process that separate ISO standards, ISO 10993, have been developed over the years to guide the need for, and means of performing, testing. For a material that has already been thoroughly tested and/or has a long history of safe clinical use in a predecessor product, little or no further testing is required. Testing usually involves sacrificing animals. Ethical standards caution against unnecessary animal testing.

Design transfer is usually viewed as the final step in the design project plan when the team agrees the product can move forward. Although design transfer to production may seem to occur at the end of the development program, in reality it has its genesis during the feasibility phase when early prototypes are crafted. Engineers must consider materials and process availability. For prototypes of small quantity manufacturing processes may be rudimentary, but as the product moves through development, the team makes prototypes which reflect the final material and methods. This is necessary so that devices qualified by way of verification and design validation truly represent the product to be marketed.

Design transfer requires that procedures and methods can ensure that the device design (that has been proven through design validation) can be manufactured. This typically translates as a final release production specification, quality control methods, and process validation. Process level failure modes and effects analysis and full process validation typify this design transfer process. As with other stages this work may not be accomplished all at once, which is why the project participants may have additional design review meetings to ensure that all design transfer requirements are met. If a future design or material change occurs, the design transfer process may be repeated in whole or in part.

Regulatory and quality team members work hand in hand to help with the understanding of limits, standards, and FDA guidance requirements and feedback from the various project reports. Regulatory submissions and examination by standards organizations may occur at various stages throughout the development program, including during clinical trials, depending upon the nature of the product. Developmental testing could be reviewed by the FDA through an Investigation Device Exemption prior to clinical trial approval and again as part of the Pre-Market Approval process (PMA). Eventually each new product or significant change will be reviewed by the FDA. This could require a premarket notification [(510(k)], a PMA, or variations on these common agency review processes.

For devices conceived in Europe, Canada, and many Pacific-rim countries, the design development programs are similar, though some key differences still exist between FDA design control regulations and the more “ISO-based” development programs. FDA does not recognize the ISO 13485 quality system operating standard in lieu of compliance with the US federal

standards for quality systems detailed in 21 CFR 820.[3] The ISO standards are not a universal medical industry standard; rather, such standards differ between countries because of different regulatory requirements. Compliance with all aspects of 21 CFR 820 is just as important today as it has ever been. FDA has never abrogated, and by law cannot abrogate, its authority for regulatory control of medical device development or manufacturing practices to any other organization, such as ISO or CEN standards. Although FDA has proposed pilot mutual recognition programs, these have only allowed a very small group of auditors based in other countries to inspect on behalf of FDA, and only if and when those same auditors have had prior successful experience in pilot-program volunteer companies.[4] Compliance with ISO 13485, in and of itself, is not sufficient to sell a product in the United States.

Medical device manufacturers strive to work with all international requirements simultaneously but in the end, each global segment may have unique requirements to be met with significant design impacts. One very typical challenge is when a device requiring electrical power must function in the U.S. with 110 volt systems but in Europe with 240 volts. Thus taking a product from one jurisdiction to another can require changes to the product already approved in a different country. Even more tedious and detailed requirements can emerge when one or more regulatory agencies adopt standard versions at different times or require modifications when adopted by their own jurisdiction. A significant example is how Canada requires its own modification of ISO 13485, proving the point that even standards are not really standardized.[5] Medical device design control standards must be researched for each country.

Post-market surveillance programs monitor returns, complaints, and clinical reports to ensure that the product and the user continue to perform safely for the benefit of the patient. These efforts are closely monitored by the US FDA and in most countries or jurisdictions where the devices are approved. Often mandatory reporting of any adverse event, regardless of where or when it may have occurred, is required. Some implantable medical devices are "tracked" directly to the patient and any explant of the device must be reported to FDA through a special database. Professionals in device monitoring are constantly trending reports of nonconformance, device failure, and customer complaints at any level, to determine if there is a need for product recall, design, or labeling changes. Some risks to the device are intrinsic to the technology: such as a battery in a pacemaker has a finite life. Some risks are associated with the medical intervention required to apply the device: such as anesthesia. Some risks may be a natural progression of the disease: such as coronary artery disease.

GLOBAL EVOLUTION OF MEDICAL DEVICE REGULATIONS AND STANDARDS

Despite years of attempting to harmonize global medical device standards, there still is not a single industry-quality-system standard or even a single standards organization that operates as a non-regulatory authority for medical device development. For example, ISO 13485:2003 is not the standard for design controls in Europe because the International Standards Organization

[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/results.cfm (last accessed February 24, 2016).

[4] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM212798.pdf (last accessed February 27, 2016).

[5] http://www.hc-sc.gc.ca/dhp-mps/md-im/qualsys/index-eng.php. (last accessed February 24, 2016).

developed this standard. Rather, this is the standard in Europe because the European Council (European regulatory authority) appointed CEN/CENELEC to adopt regulatory standards and then CEN/CENELEC chose to adopt this ISO as the applicable standard for design controls. In reality, this is a highly-regulated field in which regulatory authorities set standards in their particular jurisdictions. Efforts have been underway for decades to harmonize standards across international borders, without success to date.

In the US, The SAFE MEDICAL DEVICES ACT of 1990 amended section 520(f) of the Medical Device Law, which provided the FDA with the authority to add pre-production design controls to GMP regulations among other new requirements. FDA planned a phased implementation of the rule. It was not until October 1996 that the Federal Register issued the final rule implementing the Quality Systems Regulations to be effective June 1, 1997, and FDA allowed a one-year transition period if companies made a good faith effort to make the transition. After June 1, 1998 the FDA treated noncompliance with Design Controls the same as any other nonconformity, but only for an existing device the controls became effective with a change to changes to the device.[6]

In Europe, the Council of European Communities has the authority to regulate medical devices. In June 1993 the Council issued Council Directive 93/42/EEC for the purpose of establishing wide-ranging new regulations designed to establish a uniform standard for quality systems for the development of medical devices in the EU.[7] But the primary purpose of Directive 93/42/EEC was to ensure that medical devices would be designed to minimize risks. The "essential objectives" of the Directive are to ensure that medical devices "provide patients, users and third parties with a high level of protection and attain the performance levels attributed to them by the manufacturers."[8] Known as the Medical Device Directive, it came into effect on 1st January, 1995; but allowed a transitional period to June 1998, within which manufacturers might choose either to apply CE Marking under the terms of the Directive or to conform to specific national regulations which allowed the product to be marketed only where such national regulations were accepted. All devices to enter the market in the EU after June 13, 1998 were required to bear CE Marking.

While the Directive sets general standards, it designated the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC) as the competent bodies to adopt more specific harmonized standards for medical device quality systems. Effective February 1997, CEN/CENELEC adopted EN 46001, to be used in conjunction with ISO 9001:1994, to define the requirements for quality systems relating to the design, development, production, installation and servicing of medical devices. (ISO 9001:1994 applies broadly to industry and EN 46001 sets the more specific requirements for medical devices.) In September 1997, CEN adopted EN 1441 as the specific standard for medical device risk analysis required by Directive 93/42/EEC. CEN later replaced EN 46001 when it adopted EN ISO 13485:2003. Additionally, CEN later replaced EN 1441 when it adopted ISO 14971.

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[6] Final Rule, SMDA: Federal Register, Oct. 7, 1996, Vol 61, No 195, pgs 52602-52662.
[7] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31993L0042. (last accessed February 24, 2016).
[8] *Id*.

The Directive established that member states (countries in the EU) would certify "Notified Bodies" to be responsible to carry out detailed examinations of manufacturers and their quality systems documentation. Thus a Notified Body must ensure that quality systems standards are met before the CE Mark can be placed on the medical device. The certification must be renewed periodically.

For medical products above a certain "risk class," prior to marketing, a product must be examined to determine that it performs as intended. The performance of the product must be assessed in the context of the regulatory application for market entry. We cannot examine performance of a product without understanding the regulatory requirements because medical products cannot enter the market except by way of regulatory authority standards (norms).

In the US, the performance of the product is evaluated by way of examination of the application [510(k)] through the appropriate and knowledgeable branch of the FDA. The application contents, and thus the evidence of safety and performance for a surgical mesh, follows the FDA's standard, which is "*FDA Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh*" issued March 2, 1999. This is the only performance standard in the US for surgical mesh.

The FDA considers how well the product performs to the standards identified within the Guidance, such as sterilization testing, physical testing and shelf-life, which are parameters guided by other national standards such as Association for the Advancement of Medical Instrumentation (AAMI) and American Society for Testing and Materials (ASTM) standards, and equivalence to a predicate. When satisfied, the FDA issues the 510(k).

For Europe, the standards for performance for a new product receive their adjudication by way of examination of the Technical File through the appropriate and knowledgeable Notified Body (NB). The NB is a licensed surrogate for the regulatory authority. The Technical File is examined for completeness and the information contained therein about the performance of the product. The performance norms in this instance are identified as "essential requirements" which typically represent a litany of international standards and comparative analysis to alternative technologies or methods. Although an NB is not constrained by a published guidance document, most medical device notified bodies are well versed in their particular area of examination or will hire a consultant in the specialty to help advise on the suitability of the product's Technical File. When satisfied, the product is awarded a CE mark.

In the US, when an existing product undergoes a significant change, a new 510(k) is submitted to FDA afresh and then the product is assessed to current standards. In Europe, a device is reevaluated by the Notified Body on a periodic basis to current standards in order to retain the CE mark.

ETHICON'S DEVELOPMENT OF PROLENE SOFT MESH, GYNEMESH PS, PROLIFT, PROLIFT+M AND PROSIMA

Ethicon, like all medical device manufacturers, operates within a highly regulated and constantly changing industry that supports the evolving practice of medicine. Regulators in various countries reflect the expectations of their citizens and culture. Physicians reflect the expectations

of a demanding clinical environment. Patients increasingly expect medical devices to solve natural biological function failures with the least inconvenience and stress. Within this context a medical device is designed to enhance benefits to the majority of patients while limiting inherent and unavoidable risks. In my opinion, Ethicon has been a leader in this endeavor with implantable Prolene Soft Mesh Products.

In my opinion, the development of Prolene Soft Mesh, Gynemesh PS and Prosima by Ethicon conformed to the Design Control and Review standardized requirements as previously described. This section of my report will review the development process and provide specific examples of how these requirements were met.

History of Original Prolene Sutures and Mesh

It is important to appreciate that long before modern day design control standards came into being, Prolene was successfully developed as a suture biomaterial in the 1960s.[9] Further, Prolene also has been used as a biomaterial for other surgical mesh applications for more than 4 decades.[10] When developing the modern day design control standards, the FDA realized that provision had to be made for the fact that numerous medical devices were already on the market and had proven histories of safe and effective use in the human body. The FDA declared that the modern design controls did not warrant retroactive application to these devices. Moreover, in conducting any risk analysis concerning a new medical device, both FDA guidelines, EN 1441:1997, ISO 14971:2000, ISO 14971:2007 and ISO 10993 require consideration of the clinical history of the device or similar devices based on published literature as well as consideration of input from the user community. In that regard, as previously mentioned, Prolene had been used for decades as a biomaterial, both in sutures and hernia mesh.[11] By the late 1980s, the FDA's own exhaustive research into the use of polypropylene implant materials led to the conclusion that polypropylene is safe and effective, and that in the human body polypropylene "degradation proceeds slowly and is generally not considered clinically significant under most circumstances".[12] Further, it is important to observe that polypropylene mesh midurethral slings (*i.e.*, TVT) have become the "gold standard" or "standard of care" for patients who require surgical treatment of SUI.[13]

Notwithstanding the lengthy history of the original Prolene sutures and mesh, in the 1990s when some of the first modern day design control standards were adopted, Ethicon implemented design controls and performed risk analyses and ongoing risk management according to the new

[9] ETH.MESH.06398628-ETH.MESH.06398643; ETH.MESH.22007390-ETH.MESH.22007391.

[10] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K915774 (last accessed on February 24, 2016); ETH.MESH.06398915-ETH.MESH.06398918; ETH.MESH.06398628-ETH.MESH.06398643; ETH.MESH.22007390-ETH.MESH.22007391; ETH.MESH.05217103-ETH.MESH.05217144.

[11] ETH.MESH. 09625731-ETH.MESH.09625737 (FDA's approval letter of new drug application for Prolene in 1969); ETH.MESH.06398793-ETH.MESH.06398932 (Prolene mesh).

[12] ETH.MESH.06934664-ETH.MESH.06934688.

[13] AUGS/SUFU Position Statement on Mesh Midurethral Slings (MUS) for Stress Urinary Incontinence, January 3, 2014 (ETH.MESH.14479863-ETH.MESH.14479866). This statement is important because the mesh in TVT is made of Prolene and medical device manufacturers are required to consider the history of use of their mesh regardless of the particular application.

standards when adapting the original Prolene mesh to SUI applications. It is my opinion that Ethicon has robustly complied with the FDA's QSRs, ISO 13485, ISO 14971:2000, ISO 14971 2007 and ISO 10993 with respect to these new applications of its original Prolene mesh.

Development of Prolene Soft Mesh

In the late 1990s Ethicon sought to develop a smaller diameter mesh for additional applications. The company launched a project which resulted in a 3.5 millimeter mesh that became known as Prolene Soft Mesh, given its softer feel than the previous hernia mesh. The overriding purpose of the development of Prolene Soft Mesh was to offer a low-density monofilament material with a reduced stiffness to improve the intra-operative handling of the mesh during surgical placement.[14] Otherwise, Prolene Soft Mesh is the same as the original Prolene mesh in material, composition and indications for use.[15] Ethicon performed testing necessary to ensure that its Prolene Soft Mesh was chemically the same as its original Prolene mesh.[16] Ethicon's design history file and CE Mark files for Prolene Soft Mesh are very thorough and demonstrate compliance with the FDA's QSRs as well as the European Directive Standards.[17]

Development of Gynemesh PS

Ethicon began marketing Prolene Soft Mesh in early 2001, and by 2003 introduced Gynemesh PS, the exact same Prolene Soft Mesh but cleared for the specific indication for use of vaginal prolapse. Ethicon's design history file and CE Mark files for Gynemesh PS are very thorough and demonstrate compliance with the FDA's QSRs as well as the European Directive Standards.[18]

Gynemesh PS cleared by FDA under K013718, according to the FDA reviewer, was considered to be "*identical to Ethicon's previously marketed Gynemesh Prolene soft mesh (k001122). The only difference is a narrowing of the indication from general hernia repair to the more specific 'tissue reinforcement and long-lasting stabilization of the pelvic floor in vaginal wall prolapse'. Despite the change, the narrower indication is not a new intended use but is a subset of the previous one. The physical properties of Gynemesh Prolene appear to be sufficient for this indication. No new technological characteristics have been introduced in Gynemesh Prolene that could affect the devices' safety or effectiveness.*"[19]

Development of Prolift

By providing precut mesh and disposable delivery tools Ethicon then launched Prolift again using the exact same Prolene Soft Mesh.[20] Ethicon's design history file and CE Mark files for

[14] ETH.MESH.24910233-ETH.MESH.24910251.
[15] ETH-01646 – ETH-01715.
[16] ETH.MESH.06212061-ETH.MESH.02612333.
[17] ETH.MESH.24910199-ETH.MESH.24912944; and ETH.MESH.06399040-ETH.MESH.06399294; and ETH.MESH.06399295-ETH.MESH.06399357.
[18] ETH.MESH.00219861-ETH.MESH00221917; ETH.MESH.02225348-ETH.MESH02225631 and ETH.MESH.06400722-ETH.MESH.06401045.
[19] ETH.MESH.20070090-ETH.MESH.20070220 at pages 20070105-20070106.
[20] ETH-00950 – ETH-01228.

Prolift are very thorough and demonstrate compliance with the FDA's QSRs as well as the European Directive Standards.[21]

Development of Prolift+M

Prolift+M differs from Prolift in that the Prolene material was combined with absorbable fibers to produce a product that provides acceptable handling characteristics during implantation while meeting the goal of reducing the ultimate implant mass.[22] Ethicon's design history file and CE Mark files for Prolift+M again are very thorough and demonstrate compliance with the FDA's QSRs as well as the European Directive Standards.[23]

Development of Prosima[24]

Ethicon developed Prosima which included presized Gynemesh PS with enhanced delivery tools. Prosima was conceived by a physician, with the goal of standardizing a simpler procedure of pelvic organ prolapse repair.[25] Prosima is indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor, either as mechanical support or bridging material for the facial defect.[26] The surgical accessories provide maintenance of the vaginal canal during the period of healing following surgical repair of vaginal wall prolapse, while supporting the position of the mesh implants.

Prosima consists of Anterior, Posterior and Combined Pelvic Floor Repair Systems (both anterior and posterior configurations in one package.) Each configuration includes pre-cut Gynemesh PS implants and instruments to facilitate mesh placement and postoperative support components (removed at specific intervals after surgery.) By reinforcing the vaginal repair with mesh implant and supporting the vagina with the VSD for 3 to 4 weeks after surgery, the system is intended to reduce the risk of surgical failure and recurrent prolapse. The system counteracts intra-abdominal pressure that can adversely affect the healing of vaginal repair.

Prosima surgical tooling consists of disposable "A-Inserter", an instrument to facilitate insertion of the mesh into anterior tissue channel and a "P-Inserter" to facilitate insertion of the mesh into posterior tissue channel. A device known as a "VSD" supports the vaginal tissues for a few weeks after surgery. The VSD supports the vaginal tissues after surgery and facilitates abutment of the vaginal tissues against the Mesh until tissue ingrowth occurs. Using Prosima avoids the need for dissection outside the pelvic cavity An adjustable volume balloon with syringe is provided, as a replacement for postsurgical vaginal gauze packing to better customize the

[21] ETH-03260-ETH-07426; and ETH.MESH.06402274-ETH.MESH.06402329.
[22] ETH. Mesh.02148295-ETH.MESH.02148309.
[23] ETH.MESH.00219861-ETH.MESH00221917; ETH.MESH.02225348-ETH.MESH02225631 and ETH.MESH.06400722-ETH.MESH.06401045.
[24] I am providing a more detailed discussion of Prosima than the other Prolene Soft Mesh Products only as a demonstration of the design and development work that appears in the design history files and technical files for each of the Prolene Soft Mesh Products. My opinions regarding the Prosima device are equally applicable to the other Prolene Soft Mesh Products.
[25] ETH.MESH.00754001-ETH.MESH.00754003; ETH.MESH.00753442-ETH.MESH.00753445.
[26] ETH.MESH.02341398-ETH.MESH.02341453.

stabilization of the tissues immediately post-op. The surgical system is accompanied with extensive instructions for use and Ethicon provided for training of new users.

The basic goals of Prosima were to meet the following user needs (inputs):[27]

- Repair system that enables users to perform a standardized procedure
- All devices provided in one repair system
- Mesh implants that are pre-shaped for pelvic floor repair
- Overall procedure is suitable for all levels of surgeon experience with mesh-based PFR
- Implant placement does not require blind passages
- Mesh implant that requires minimal handling
- Mesh implant that is easy to place
- Device designed to abut mesh implant to vaginal wall
- System components are adjustable to fit patient population
- System components designed to maintain the vaginal caliber and fill the space
- System components designed to maintain correct anatomic position
- System components designed to reduce potential for vaginal canal adhesions
- System components are easily placed and removed
- Procedure that is designed to avoid unintended trauma
- Packaging system shall keep system components organized

Per the Ethicon development procedures, these user inputs were converted to a Design Requirements Matrix as part of the overall Project Plan.[28] This detailed design requirement document was periodically updated and refined as additional information was obtained.[29] The Project Team conducted periodic design reviews.[30] The Project Team also conducted various risk analyses for Prosima including design FMEAs, process FMEA and application FMEA.[31] In my opinion, all of the Prosima design controls including project plan, design inputs, design outputs, design reviews, risk analyses, design verification and design validation exercises were methodical, robust and properly incorporated into the Design History File.[32] These are the very same design controls that were created as the industry standards to ensure that the system would be safe and effective.

Ethicon was careful not to alter the mesh component of Prosima. Thus, at the various stages of the design and development of Prosima, Ethicon referred back to the design and development of Prolene Soft Mesh and Gynemesh PS as the basis for ensuring that the mesh component of

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[27] ETH.MESH.01590336XLS; ETH.MESH.06708627-ETH.MESH.06708645.

[28] ETH.MESH.06708109-ETH.MESH.06708117; ETH.MESH.01590336XLS (Version A); ETH.MESH.01590364XLS (Version B); ETH.MESH.01593769XLS (Version C).

[29] *Id.*

[30] ETH.MESH.01594038-ETH.MESH.01594097; ETH.MESH.01591871; ETH.MESH.00754107-ETH.MESH.00754125; ETH.MESH.01593721-ETH.MESH.01593753.

[31] An FMEA, or Failure Modes and Effects Analysis, "is a technique by which the consequences of an individual fault mode are systematically identified and evaluated. . . . Components are analysed one at a time." ISO 14971:2007 at p. 57. An FMEA may be performed for the design of a product (dFMEA), the manufacturing process (pFMEA) or the use of a product (aFMEA).

[32] ETH.MESH.24910199-ETH.MESH.24912944.

Prosima met all applicable industry standards for the design of safe and effective medical devices.[33] Given that the mesh component of Prosima is identical to Prolene Soft Mesh and Gynemesh PS, in my opinion it was proper for Ethicon to rely on data for Prolene Soft Mesh and Gynemesh PS as the part of the documentation for compliance with the industry standards.

ADDITIONAL AFFIRMATIVE OPINIONS AND REBUTTAL TO RUSSELL DUNN'S OPINIONS

1. **Ethicon's Quality Systems for Its Prolene Soft Mesh Products Are Robust and Meet or Exceed Industry Standards**

Dr. Dunn asserts that the design processes for the Prolene Soft Mesh Products resulted in a flawed design. In my examination of the documentation of the development process the team was diligent in all respects for the evaluation of the Prolene Soft Mesh Products to ensure the properties of the mesh were as robust as necessary for its intended use. Indeed, the Ethicon procedures, followed by the project team, met or exceeded industry norms for Design Control and Review as I will illustrate below.

On page 20 of Dr. Dunn's report he provides a tutorial about "stage-gating" and leaves the impression that Ethicon did not adequately perform a phased development program according to industry standards. For a medical device manufacturer, development is guided by FDA regulation CFR 820.30 and 820.40 for Design Control and Review, and for companies doing business in Europe and some other countries, the requirements in ISO 13485, Section 7.3. Dr. Dunn purposefully linked the product development phases and the risk management work conducted by the design team and alleges (page 19):

> *"2) Ethicon did not prior to launch, or has not to date, considered oxidative degradation as a potential failure mode for their Prolene PP Gynemesh products. . . .*
>
> *3) Ethicon has not investigated oxidative degradation of its Prolene polypropylene in their Prosima, Prolift and Prolift+M product's risk analysis. Had this potential failure mode been considered, it would have led to an evaluation of the risk of injury associated with this type of failure and would also have led to testing that assessed both the frequency and severity of it.. . . .*
>
> *4) The risk analysis associated with oxidative degradation of the Prolene-based component of the Prosima, Prolift and Prolift+M devices was not adequately measured or assessed in terms of possible failure modes, frequency of occurrence, in terms of changes to mechanical properties, and in terms of the potential for harm caused prior to when this product was placed on the market; these deficiencies are lacking to this day.*
>
> *5) The design of the Prosima, Prolift and Prolift+M devices was faulty [or defective] in that Ethicon . . . did not eliminate or mitigate the resulting risk of harm . . . ."*

[33] ETH.MESH.01412964.XLS; ETH.MESH.01412514-ETH.MESH.01412516; ETH.MESH.01412596-ETH.MESH.01412600.

To understand that Dr. Dunn distorts the documentation contents and project results, it is important to examine the Design Control and Review practices (including the Risk Management program) that Ethicon (and its contractors) undertook for the Prolene Soft Mesh Products. I have examined the results of the Design Review meetings and the "deliverable" documents required under the aforementioned regulations and standards and find that in fact, Ethicon most certainly managed the Design History Files, the associated Technical Files (required for Europe), and the development processes, as well as risk management processes, according to regulations and standards.

Before detailing my findings, I will clarify the differences between "stage gating" that Dr. Dunn referred to (which is a generic industrial method) and the internationally recognized Design Control and Review requirements for medical devices.

> According to the website for the Product Development Institute Inc. 2000-2012 (Product Development Institute Inc. and Stage-Gate International are registered trademarks) we find that: "Many businesses use the Stage-Gate® process—which this author [sic] introduced in 1988—to conceive, develop, and launch new products. As proficient companies have implemented, modified, adapted, and improved the methodology, it has morphed into a faster, leaner, and more effective tool. The next generation process, or NexGen Stage-Gate, builds in seven principles of lean, rapid, and profitable new-product development to maximize productivity in product innovation."[34] In other words, "stage-gating" is a proprietary program promoted by a commercial entity. "Stage-gating" calls for seven stages: 1. Customer focused, 2. Heavy front-end homework before development begins, 3. Spiral development—loops with users throughout development,4. Holistic—effective cross-functional teams, 5. Metrics, accountable teams, profit/loss reports for continuous learning, 6. Focus and portfolio management, 7. Lean, scalable, and adaptable.

In contrast medical device Design Control and Review is not a proprietary program and is the standard for the medical device industry worldwide. The US FDA regulation 21 CFR 820.30 (and 820.40 for document control) establish the means whereby developers ensure the adequacy of the design requirements and ensure that the design released to production meets the approved requirements. FDA regulations do not dictate specific phases but recognize the need for adequate design and development planning, to include appropriate phases for the project at hand. The fundamental difference between the "stage-gating" theory and Design Control and Review regulations is the FDA emphasizes that "outputs meet the inputs" and demonstration that adequate transfer of the idealized design to production systems. FDA regulations do not dictate the steps or phases but instead focus on how the design team ensures the delivery of product quality. Unlike "stage-gating", the FDA regulations are not concerned with "rapid and profitable new product development." Thus it is all together fitting that Ethicon conformed to recognized medical device development requirements, irrespective of a commercial program called "stage-gating". All of the elements of design and development that are described by Dr. Dunn in his report on page 20 were in fact met by Ethicon, including robust risk management and detailed Design Transfer. I have summarized below the Prosima development documentation compiled over many years. Later in this report I summarize the risk management program that was part of

[34] www.**stage-gate**.net/downloads/working_papers/wp_23.pdf (last accessed February 29, 2016).

this development program, and show that Dr. Dunn's allegation that Ethicon failed to evaluate potential harms is also without foundation.

Dr. Dunn detailed that the following elements are required in a good development program. Using Prosima, I have shown below that all of these elements were met by the Ethicon development management process:

(1) Customer needs, market assessment, and the development of a risk assessment.

(2) Feasibility, including validating the product concept, building a business case, updating the market assessment, examining the health-safety concerns, etc.

(3) Design, including product specification, a feasibility of the manufacturing, updating of market assessment, competitive analysis, and health and safety. (Risk Management is discussed below)

(4) Verification, including testing all the requirements of the product to assure the product meets the design requirements. All results are documented.

(5) Manufacturing. develop a process to manufacture the product that meets the product specifications set in the design phase, including a quality-assurance plan

(6) Product Field Activity, including validating product performance and function in the field, and analyzing results, including the FMEAs (various), labeling and warnings or if other remediating actions are required.

Concept team meeting August 22, 2004, memo September 7, 2004:[35] This meeting brought the original team together to evaluate the project scope and procedure. The team discussed the "stabilizing card" and graduation marks. The shape of the "legs" were defined, orientation of the blue lines and the characteristics of the delivery card were discussed. This meeting also laid out various instrumentation and delivery components for the surgical procedure.

Project Plan: MINT (working name for Prosima) Date June 13, 2005:[36] This laid out the project plan, team members documented approvals (signatures and dates). These are required project plan elements. The plan defined the value of the project as establishing a less technically challenging and standardized surgical procedure which minimized dissection and could be less time consuming, and which might use less mesh. The plan identified product attributes that were critical to quality as device size and shape, material selection, intra-vaginal pressure distribution, number of procedural steps, user skill level required, tissue tunnel size and shape. The project plan clearly stated that the procedure and instrumentation components were to maintain the shape and form of the vagina for the critical period of the initiation of tissue in-growth to allow the tissue to grow properly into the mesh without undesired mesh repositioning (a known post-operative complication.)

[35] ETH.MESH.06708470-ETH.MESH.06708473.
[36] ETH.MESH.06708171-ETH.MESH.06708179.

Biocompatibility Strategy for Prosima:[37] This strategy required that the team supply a bill of materials for the device, including any materials used in processing. Key assumptions in this plan were the type of indication for use, sterilization method. The report lists all the components expected to be in the system. The plan required confirmatory cytotoxicity testing and that the entire mesh/template/film assembly was to be tested. The plan states the assumption that there is no mesh/template interaction due to manufacturing/processing, packaging and cutting. The plan called for biocompatibility testing of all other components if the materials were not previously approved materials. And finally, the strategy required a final biocompatibility plan when the final materials for the components and processes had been selected. These were all met.[38]

As previously discussed the Design Input Requirements were reviewed on numerous occasions. For example, Review 08-21-06:[39] team review of the design requirements matrix to fulfill Ethicon PR800-011 and FM-0000475. The minutes of the meeting were published 09-21-06. The team reviewed document DRM 082305 Design Inputs Rev A and created a list of action items.

Periodic Design Review Meetings with agenda, minutes, team members identified, independent reviewer identified. These review meetings incorporated the results from numerous design transfer sub-projects at various manufacturing locations:

January 23, 2007	Listed prior design review; described updated strategy documents, reviewed design requirements matrix	ETH.MESH.01590654; ETH.MESH.01412766
February 1, 2007	Reviewed project scope; action items from prior meeting, design requirements matrix elements; plans for quantitative testing and results; statistical plan; strength testing of the mesh; dimensional confirmation; cadaver lab study; biocompatibility risk assessment, kit configuration; plans for design validation; design review deliverables checklist	ETH.MESH.00754143 ETH.MESH.01590775
February 28, 2007	Design packaging validation results; action items reviewed; design requirements matrix; quantitative and qualitative testing; instructions for use; verification and validation testing, FMEA and risk assessment updates	ETH.MESH.01412768 ETH.MESH.01593971
March 16, 2007	Design Validation, including packaging; cadaver trials; clinical expert report for CE marking	ETH.MESH. 00754107 ETH.MESH.01412708

[37] ETH.MESH.06708062.
[38] ETH.MESH.01412514-ETH.MESH.01412526.
[39] ETH.MESH.00754022; ETH.Mesh.01412602; ETH.MESH.01412636, ETH.MESH.0141260, ETH.MESH.01590320.

April 9, 2007	Design Requirements Matrix, Pilot builds, transportation testing, stability, regulatory requirements, specific mesh handling requirements; risk assessment; design review checklist action items;	ETH.MESH.00754134 ETH.MESH.01590440
April 19, 2007	IFU change and design validation of changes; prep for clinical evaluation units; design review checklist; design verification and validation task review	ETH.MESH.00753412 ETH.MESH.01593683
May 30, 2007	Balloon functionality requirement & testing, process flow, pFMEA, and process control plan, validation activities, post balloon PQ activities, updated design transfer checklist, high level process review of all components and kitting	ETH.MESH.00753874 ETH.MESH.00754074 Eth.MESH.01411673 ETH.MESH.01411692 ETH.MESH.00753878
June 6, 16, 26 and June 28, 2007	Specific process and pFMEA review prior to design review #9, Reviewed action items, design requirements matrix, stability testing, transportation testing, design for environment, instructions for use,	ETH.MESH. 00753881 ETH.MESH.00754077 ETH.MESH.00754089 ETH.MESH.00754145 ETH.MESH.01591116 ETH.MESH.00754092 ETH.MESH.00754202 ETH.MESH.00754203 ETH.MESH.01590037
July 16, 17, 19, 2007	Agenda and meeting objectives memo, Meeting minutes for Design Transfer checklist, and contractor design transfer, and review meeting for design history file content, confirmation of action item closure	ETH.MESH. 00754071 ETH.MESH.00754081 ETH.MESH.00754087 ETH.MESH.00754105 ETH. MESH.01412705 ETH.MESH.00754086

Ample documentation demonstrates the diligent and regulatory-compliant design and development activities, including design transfer to production, conducted by Ethicon employees, manufacturing locations and contractors to ensure that Prosima (inclusive of the Prolene soft mesh) met customer requirements. The documentation shows that project development management incorporated all of the design control elements Dr. Dunn said were necessary, but which Dr. Dunn failed to acknowledge in his report.

Dr. Dunn is cavalier is his accusation that Ethicon has an inadequate Quality System when he states: "*All of these things and more are evidence that the Quality Systems at Ethicon are inadequate*," but this claim has no merit; nor does Dr. Dunn seem to understand the scope of the Ethicon Quality System.

Ethicon's Quality Systems are repeatedly examined and approved by auditors from numerous countries and have been refined over decades to stay current with industry standards.[40] The system robustly feeds back field experience and Clinical Expert Reports to ensure the company responds to not only the intended use by design, but also the field experiences.

Dr. Dunn may not be aware that for moderate risk medical products, the safety of the product, after the initial application for market entry, is primarily monitored through the intertwined practice of Quality Systems which must meet the requirements established by numerous regulatory authorities; for example:

- In the US, the standards for Quality Systems are set forth in the Code of Federal Regulations 21 Part 820, sometimes called cGMPs-i.e. "current". These standards were previously known as "Good Manufacturing Practices." The over-arching purpose of 21 CFR Part 820, as stated in the regulation, is "to ensure that finished devices will be safe and effective." The current regulations go beyond manufacturing to incorporate multiple levels of management oversight, design controls, self-auditing, purchasing controls, traceability and recordkeeping. These quality system standards also require post-market monitoring through complaint handling and adverse event reporting. Reports of component or product nonconformance require strict oversight and an active corrective and preventive operation. These are obligations far beyond the already strict development process requirements. The medical device manufacturer is subject to evaluation by government inspectors and auditors, not to mention required internal periodic reports to management. Companies may even hire outside auditors to help ensure unbiased appraisal of the methods which ensure oversight to the requirements. All of this nearly constant oversight is intended to ensure compliance to national and international norms that monitor product safety. Failure to meet government inspection norms can result in

[40] See, e.g., ETH.MESH.07281437-ETH.MESH.07281458; ETH.MESH.02252211-ETH.MESH.02252224; ETH.MESH.06398762-ETH.MESH.06398792; ETH.MESH.11818939 ETH.MESH.06400993-ETH.MESH.06401045. FDA inspections show that Ethicon, like all medical device manufacturers, does not have a perfect audit record. However, they also show that no deficiency has been observed with respect to Dr. Dunn's opinions concerning risk analyses regarding the subject of degradation.

serious consequences for the company and suspension of the product from the market. FDA takes the most drastic steps if safety is compromised.

- To sell medical devices in Europe and to hold a CE Mark, a manufacturer today must have evidence of conformance to ISO 13485:2003, but this has not always been the case. In the past the Notified Body would have examined the quality system to EN 46001, but now the technical oversight to the current standard is handled by an ISO registrar, who may or may not also be a Notified Body. These auditors examine the company's quality system and cite recommendations for corrective actions to bring specific elements of the quality system into more perfect alignment with the standards and current practices. (The 2003 version of ISO 13485 is more closely aligned with 21 CFR 820 but FDA requirements for complaint management are more rigid, to name just one difference as an example.) If the auditor cannot confirm conformance to ISO 13485, and the company fails to make necessary corrections, the CE Mark will not be renewed. Dr. Dunn's opinion that Ethicon's Quality Systems are lacking contradicts the express findings by the independent auditors who continue to renew Ethicon's CE Mark.

2. Dr. Dunn's Opinion that Ethicon Failed to Provide Feedback Is Wrong

Dr. Dunn opined that Ethicon failed to provide "feedback" to the FMEA process. In particular, he opined that Ethicon "did not have a quality system in place to address complaint handling, investigation, and appropriate responses to complications and issues as they relate to oxidative changes to polypropylene."

Dr. Dunn overlooked that not only did the team "feedback" to the risk management program from "other tools," the team actually began the Prosima development program and risk management assessments with a review of prior similar products.[41] Memo to file RMR-0000029 in April 2007, documented the general complaint review of GYNECARE pelvic floor repair products in support of the Prosima development project.[42] The data from the analysis tables provided valuable field-based information to be used in the assessment of harms and hazards for the Prosima product line, and to "populate and validation risk management tools such as FMEAs and RMRs on the Prosima project." The data from the predicate device complaint review initiated the original Risk Management Report.[43]

In addition, Ethicon specifically evaluated on a continuing basis the performance of its Prolene mesh and Prolene Soft Mesh Products.[44] Known as Literature Reviews, Clinical Expert Reports,

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[41] ETH.MESH.01590642-ETH.MESH.01590645.
[42] *Id.*
[43] ETH.MESH.01590632-ETH.MESH.01590637 and ETH.MESH.00759120-ETH.MESH.00759125.
[44] ETH.MESH.00220026-ETH.MESH.00220041; ETH.MESH.00220004-ETH.MESH.00220025; ETH.MESH.06399183-ETH.MESH.06399184; ETH.MESH.00753832-ETH.MESH.00753835; ETH.MESH.01954198-ETH.MESH.01954203; ETH.MESH.03711785-ETH.MESH.03711791; ETH.MESH.02148295-ETH.MESH.02148309; ETH.MESH.06400898-ETH.MESH.06400921; ETH.MESH.06398644-ETH.MESH.06398666; ETH.MESH.06398630-ETH.MESH.06398643; ETH.MESH.01784823-ETH.MESH.0178; ETH.MESH.00353635-ETH.MESH.0035; ETH.MESH.10178882-ETH.MESH..

Clinical Evaluation Reports and/or Complaint Reviews, it is the obligation of the company to compile, analyze and report worldwide statistics concerning complaints, adverse event reports and medical literature publications to obtain the CE Mark application. These compilations are an important step in the process of assuring post market that a medical device performs as expected and is safe. Over the years, Ethicon has stayed abreast of the clinical literature and conducted periodic Literature Reviews, Clinical Expert Reports, Clinical Evaluation Reports and Complaint Reviews concerning Prolene Soft Mesh Products.[45] None of these reports includes any finding that oxidative degradation has created a clinical hazard. Moreover, Dr. Dunn has not cited any reports where oxidative degradation of the Prolene meshes has created a clinical hazard.

In short, Ethicon has robust methods in place for acquiring and analyzing the performance of products in clinical evaluations as well as after-market introduction. The company makes this information available for new product development programs and monitors the hazards from both intended use and inadvertent use. Reporting of adverse events is public through the Medical Device Reporting and through various worldwide clinical experience reports. There were no reported clinical incidents whereby there was even a suggestion that mesh oxidation or polypropylene degradation of any kind would be the root cause for the reported incident. Dr. Dunn has not provided any examples of how Ethicon may have failed to deploy their extensive quality management system for the Prolene Soft Mesh Products.

3. Dr. Dunn's Analysis of Oxidative Degradation as a Failure Mode or Hazard of Prolene Soft Mesh Products Contradicts Industry Standards

Dr. Dunn distorts the documented facts by his assertion that:"*the risk analysis associated with oxidative degradation of the Prolene-based component of the Prosima, Prolift and Prolift+M devices was not adequately measured or assessed in terms of possible failure modes, frequency of occurrence, in terms of changes to mechanical properties, and in terms of the potential for harm prior to when this product was placed on the market; these deficiencies are lacking to this day."*

He alleges that oxidative degradation of the Prolene polypropylene mesh in the Prolene Soft Mesh Products was a potential failure mode that "[should]*have led to an evaluation of the risk of injury*.

At one point Dr. Dunn identifies oxidative degradation as a "failure mode." At another point he identifies oxidative degradation as a "hazard." At still another point he identifies oxidative degradation as a "risk." Then he says that oxidative degradation has a "resulting harm." All of these different characterizations occur on the very same page of his report. These statements demonstrate Dr. Dunn's severe lack of understanding of medical device industry standards, including ISO 14971.

To appreciate Dr. Dunn's misdirection we need to define some basic terms that have been used in hazard analysis and risk assessment for decades:

[45] *Id.*

Failure Mode - ***effect*** by which a failure is observed in a system component.[46]

Hazard - potential source of harm.[47]

Harm - physical injury or damage to the health of people, or damage to property or the environment.[48]

Risk - combination of the probability of occurrence of harm and the severity of that harm.[49]

According to the Ethicon risk analysis procedure "Potential Failure Mode" is "a specific manner that the medical device or element of the medical device being evaluated will fail to perform one or more of its intended functions."[50] The medical device industry generally recognizes that to have an "effect" (e.g. adverse event) one must have a "failure mode". The identification of a failure mode depends on an understanding of the design requirements. Thus, failure modes would include failures to achieve design requirements such as tissue ingrowth, biocompatibility and mechanical integrity. Dr. Dunn's passion for oxidative degradation notwithstanding, he has not shown how oxidative degradation has led to any failure to perform the intended function - - bridge for tissue in-growth.[51]

A design level FMEA starts with the question: what hazard could occur if the product failed to meet a specific design requirement. As an example, the Ethicon team followed the proper steps to this analytical method: (1) the pertinent design requirements were identified; (2) they were analyzed in detail; (3) the mesh requirement to promote tissue ingrowth was analyzed; (4) the team recognized that if there was a failure to promote tissue ingrowth that the hazard could be severe.[52] However, there was no historical evidence that oxidative degradation would or could cause the mesh not to perform its intended functions. Had there been, then the team would have conducted further analysis. Dr. Dunn has improperly opined that the team should have analyzed oxidative degradation as a "cause" for which there was no known clinical hazard and no observed clinical failure mode as explained below.

Dr. Dunn has not linked oxidative degradation to an observed failure mode (clinically observed effect) for Prolene meshes. At best, it could theoretically be a "cause" of a potential failure mode (such as loss of mechanical integrity or lack of biocompatibility) but the product history simply does not support this theory. The fundamental problem with Dr. Dunn's characterization of oxidative degradation as either a failure mode or the cause of a potential failure mode is that his report nowhere identifies any instance where oxidative degradation has caused a Prolene mesh to fail to perform according to its design requirements in the human body.

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[46] IEC 812 *Standard for Analysis Techniques for System Reliability- Procedure for failure mode and effects analysis* 1985
[47] ISO 14971.
[48] *Id.*
[49] *Id.*
[50] ETH.MESH.10619196-ETH.MESH.10619223.
[51] ETH.MESH.02341398-ETH.MESH.02341453.
[52] ETH.MESH.06399227-06399244 and ETH.MESH.06399211-06399225; ETH.MESH.06398793-ETH.MESH.06398932; ETH.MESH.16046418-ETH.MESH.16046866.

Moreover, Dr. Dunn has not identified any harm associated with oxidative degradation. The purpose of an FMEA is to assess the severity and frequency of occurrence of harms associated with a failure mode. It is impossible to assess the severity and frequency of occurrence (risk) of an unidentified harm.

4. **Dr. Dunn's Concerns over Oxidative Degradation of Prolene Meshes Are Flawed Because They Ignore the Fulfillment of the Essential Purpose of the Meshes**

Dr. Dunn's report nowhere analyzes how oxidative degradation could have impact on the essential purpose of Ethicon's Prolene Soft Mesh Products. Even if his opinions concerning oxidative degradation were correct and at some unknown future time (he acknowledges that the potential impact is at some future time) the mesh undergoes some amount of oxidative degradation, the effect would have no significance because the mesh would have already fulfilled its essential purpose. In performing their analysis, Ethicon engineers were well aware that the primary function of Prolene Soft Mesh is to provide a bridge for tissue incorporation for strengthening weakened natural tissues.[53] This primary function goes back to the original hernia mesh applications. These same engineers were aware that tissue in-growth occurred reasonably soon after implantation (weeks to months) and that the tissue within the pores would soon take over the reinforcement function: the underlying reason to implant the mesh. Thus, after the tissue in-growth the strength of the mesh was of less concern. In fact, the Prolift+M System is a case in point. Ethicon developed Prolift+M using Ultrapro Mesh, which is a combination of Prolene mesh and an absorbable component. The specific purposes of Ultrapro was as a mesh that would partially degrade. Clearly, reduction in mesh strength in a normal biologic environment after tissue healing occurs is not viewed as a defect; it can be viewed as a design attribute.[54]

5. **Ethicon's Risk Analyses of Prolene Soft Mesh Products Have Been Thorough**

Dr. Dunn alleges that Ethicon did not follow requirements to pay attention to: *compatibility with relevant substances and compatibility with tissues or body fluids.* The short answer is that Dr. Dunn is wrong. As discussed below, Ethicon conducted numerous analyses of compatibility.

a. FMEAs and DDSAs

There were no aspects of the use of Prolene Mesh and Prolene Soft Mesh that have not been extensively analyzed. As previously noted, prior to the latter part of the 1990s there were no medical device industry standards requirements to perform FMEAs, and in fact, FMEA is still one of many methods suggested for analyzing risks: it is not mandatory to use an FMEA as the risk analysis tool. That is not to say that there were no efforts to control risks of medical devices. In fact, dating back to the 1970s the FDA had an extensive process for premarket approval of medical devices and major companies like Ethicon were required to undergo extensive new product program reviews. When the new QSRs, including requirements for risk analyses, were adopted in the latter 1990s, previously approved and marketed medical devices were exempted

[53] See, e.g., ETH.MESH.02341398-ETH.MESH.02341453.
[54] ETH.MESH.01595614-ETH.MESH.01595753.

from Design Controls and design level risk analysis unless and until future modifications were made to the devices.[55]

Even before the new standards were adopted and even though legacy devices were exempted from design controls, Ethicon was performing risk analyses. For example, in 1995 Ethicon was performing risk analyses even for its legacy devices, including Prolene meshes, taking into account prior clinical experiences.[56] This analysis expressly considered biological incompatibility. At that time, analysis of the possibility of biological incompatibility was guided by ISO 10993-1, which expressly included the subject of biodegradation (which includes chemical reactions such as oxidative degradation).

An overriding guiding principle is now stated in ISO 10993-9:

> The level of biological tolerability of degradation products depends on their nature and concentration, and should be primarily assessed through clinical experience and focused studies. For theoretically possible, new and/or unknown degradation products, relevant testing is necessary. For well-described and clinically accepted degradation products, no further investigation may be necessary.

ISO 10993-9 further emphasizes limitations on the need for further testing as follows:

> It is neither necessary nor practical to conduct degradation studies for all medical devices. Consideration of the need for degradation studies is provided in annex A. The assessment of the need for experimental degradation studies shall include a review of the literature and/or documented clinical experience. Such a study can result in the
>
> conclusion that no further testing is needed if the product under consideration has a demonstrated history of acceptable clinical experience, new data, published data and analogies with known devices, materials and degradation products.

In the case of polypropylene as an implant material, by 1990 it was already well-known, studied and published that polypropylene is well-tolerated within the human body, and that any oxidative degradation proceeds slowly and is not clinically significant. Dr. Dunn's report improperly ignores ISO 10993, ignores the clinical history of the use of polypropylene as an implant material, and ignores the thorough studies that contradict his opinions.

One of the key reasons for emphasis on past clinical experience is that biodegradation studies involve the use of animals, but for ethical reasons there is an expressly stated goal to minimize the use of animals for testing.[57]

In the USA, the recognition of this standard is even further limited. The US FDA reserves the final decision on whether degradation studies are needed by stating categorically that the

[55] Federal Register, October 7, 1996, Volume 61 Number 195, pages 52601-52662 and in particular page 52616; see also Federal Program 7382.845, Inspection of Medical Device Manufacturers at Part III, pages 12-13.
[56] ETH.MESH.06398793-ETH.MESH.06398932.
[57] See, e.g., ISO 10993-1 at pp. 11 & 15.

appropriate division of CDRH should make the determination for additional degradation studies, not Ethicon or someone such as Dr. Dunn or myself:[58]

> **Extent of Recognition:**
>
> Complete standard with the following exceptions:
>
> Annex A - The final decision on whether degradation studies are needed should be determined by the appropriate CDRH Division.

Ethicon concluded that no further degradation studies were needed for its Prolene meshes. Ethicon properly applied ISO 10993 by factoring into its determination the lengthy history of safe clinical use of Prolene in sutures and meshes. The FDA has repeatedly reviewed Ethicon's biocompatibility risk assessments each time Ethicon has submitted 510(k) applications for each new or modified product that includes Prolene mesh and has not requested any additional degradation studies. It is my opinion, based on my years of experience with evaluating the verification, validation and risk assessment of devices and materials for implantation in the body, the application of ISO 10993 for biomaterial qualification, and working as a liaison to numerous regulatory applications around the world, that no further degradation studies were needed for Ethicon's Prolene meshes.

In 1997 in anticipation of obtaining the new CE Mark for its Prolene Mesh, Ethicon undertook efforts to demonstrate compliance with the Essential Requirements of the European Medical Directive. Ethicon documented its compliance in great detail including a risk assessment that specifically included a biocompatibility risk analysis based on detailed reports on biocompatibility testing and biocompatibility literature review as per ISO 10993 standards, and including product risk analysis and clinical history literature review as per the applicable European standard EN 1441.[59] Ethicon specifically determined that no further biocompatibility testing was needed pursuant to EN 30993, or ISO 10993. In my opinion, Ethicon properly performed all of the testing, and risk analysis, according to industry standards. In 2000 in connection with the development of Prolene Soft Mesh, Ethicon performed additional risk analyses that specifically again considered whether biodegradation could be a potential hazard.[60]

In 2001 Ethicon performed an additional risk analysis in connection with the TVT product.[61] The analysis included the Prolene Mesh component of the product. In 2001 in connection with the development of Gynemesh PS (Prolene Soft Mesh for the specific indication of use for pelvic

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[58] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/detail.cfm?standard__identification_no=31650 (last accessed February 24, 2016).

[59] ETH.MESH.16046418-ETH.MESH.16046554.

[60] ETH.MESH.06399227-06399244 and ETH.MESH.06399211-06399225. These and other risk analyses were in the form of a device design Safety Assessment or DDSA as opposed to an FMEA. There is no requirement in the industry standards that the risk analysis be in one form or the other. Either can suffice.

[61] ETH.MESH.10587931-ETH.MESH.10587950.

floor repair), Ethicon performed yet another risk analysis that specifically considered again whether biodegradation could be a potential hazard.[62]

In 2002 and 2003 Ethicon performed additional risk analyses for the Gynemesh PS mesh, again specifically considering whether any new information warranted any further consideration of whether biodegradation could be a potential hazard.[63]

In 2005 in connection with the development of Prolift, Ethicon performed another risk analysis that yet again considered whether any new information warranted any further consideration of whether biodegradation could be a potential hazard.[64]

In each and every one of these analyses Ethicon properly concluded that no further degradation studies or testing was needed because the long history of safe clinical use of Prolene mesh had adequately demonstrated that biodegradation was not a clinically significant risk.

In 2007 Ethicon performed a risk analysis for Prosima.[65] Instead of yet again analyzing the risk associated with the mesh implant material, this risk analysis expressly incorporated the findings of the prior risk analyses because again the Prolene mesh was indicated for the same intended use (tissue support) and had the same fundamental design requirements.

As discussed elsewhere in this report Ethicon conducted periodic complaint reviews, literature searches, clinical expert reviews and clinical evaluations of Prolene Mesh, Prolene Soft Mesh, Gynemesh PS, Prolift, Prolift+M and Prosima according to company procedure, analyzing any new information that would indicate a need for further analysis of risks. The continuous device performance surveillance demonstrated by Ethicon confirms there is no reason for concern that Prolene mesh oxidation presents any hazard from biodegradation.

b. Biocompatibility Risk Assessments

Dr. Dunn's opinion that Ethicon has not adequately considered the potential for oxidative degradation of Prolene in the human body is belied by the many analyses discussed above as well as the following occasions where Ethicon has conducted biocompatibility risk assessments.

Dr. Dunn's report failed to acknowledge the exhaustive biocompatibility review that the FDA provided to Ethicon in 1990 wherein based on its own independent research the conclusion was reached that (1) any oxidative degradation of the polypropylene polymer "proceeds slowly and is generally not considered clinically significant under normal circumstances" and (2) "the cumulative risk of nonabsorbable polypropylene surgical suture breakage is small, and its ability to function properly is uncontested."[66]

[62] ETH.MESH.00220317-ETH.MESH.00220330.
[63] ETH.MESH.00220303-ETH.MESH.00220316; ETH.MESH.02225455-ETH.MESH.02225470.
[64] ETH.MESH.06700941-ETH.MESH.06700967.
[65] ETH.MESH.01412964.XLS.
[66] ETH.MESH.06934664-ETH.MESH.06934688.

Dr. Dunn's report failed to acknowledge Ethicon's own internal biocompatibility risk assessment supported by detailed literature review back in 1997 discussed above.[67]

Dr. Dunn's report failed to acknowledge Ethicon's biocompatibility risk assessment performed in 1999 for Prolene Soft Mesh.[68]

Dr. Dunn's report failed to acknowledge Ethicon's biocompatibility risk assessment performed in 2000 for TVT.[69]

Dr. Dunn's report failed to acknowledge Ethicon's biocompatibility risk assessment performed in 2001 for TVT-L.[70]

Dr. Dunn's report failed to acknowledge Ethicon's biocompatibility risk assessment performed in 2002 for Gynemesh PS.[71]

Dr. Dunn's report failed to acknowledge Ethicon's biocompatibility risk assessment performed in 2005 for Prolift.[72]

Dr. Dunn's report also failed to acknowledge the detailed "Biocompatibility Risk Assessment: Prosima Pelvic Floor Repair System (Mint) report".[73] The Prosima Biocompatibility Risk Assessment, as well as the prior assessments discussed above, follows ISO 10993-1 and the FDA General Program Memorandum G-95 (the FDA guidance for biocompatibility in effect at that time.) The report refers to the mesh material as "component 1" It identifies the Prolene Soft Mesh (K013718) as the base mesh and identifies the manufacturing modifications made to the mesh during Prosima manufacturing. These manufacturing processes had been separately analyzed for potential affects to the basic mesh material. For example, the chemical equivalency of the welded and cut edges to naïve mesh had been studied previously: Chen, K. Extractables/Leachables of the Ultrasonic Welded Polypropylene Mesh Pockets for Project Mint. RCPC-111606-KC.2006.[74]

Based upon the clinical indication for use, the packaging and contact materials in the kit, the method of sterilization and the biologic environment into which the Prolene Soft Mesh was to be implanted and according to recognized standards, no further biocompatibility risk assessment was warranted on this material. Apparently both the US FDA and the Notified Body British Standards Institute (BSI) agreed with this biocompatibility risk assessment since neither party requested any additional biocompatibility analysis during the premarket reviews conducted independently, and on numerous occasions, by these organizations.

[67] ETH.MESH.16046418-ETH.MESH.16046554.
[68] ETH.MESH.22007390-ETH.MESH.22007391.
[69] ETH.MESH.00349226-ETH.MESH.00349237.
[70] ETH.MESH.00349224-ETH.MESH.00349225.
[71] ETH.MESH.22007389.
[72] ETH-03891 – ETH-03897.
[73] ETH.MESH.01412514-ETH.MESH.01412526
[74] ETH.MESH.04946427-ETH.MESH.04946432.

Conclusion Concerning Biocompatibility Risk Assessments: There is adequate documentation to demonstrate that the Ethicon development team did consider the specific use of Prolene Soft Mesh in this specific indication for use, inclusive of the potential impact from manufacturing processes and the potential interaction from other materials that would be in contact with the mesh from manufacturing through to the surgical procedure. And in fact, Ethicon clearly paid proper attention to: *the compatibility between the materials used (Prolene polypropylene) and biological tissues, cells and body fluids, taking account of the intended purpose of the device."*

6. Ethicon Properly Completed Its Risk Analysis Worksheets

Dr. Dunn opines that Ethicon failed to properly complete worksheets during its risk analyses. Dr. Dunn apparently misunderstood the scope of the DDSA. For example, the Gynemesh PS DDSA was conducted for the purpose of analyzing the new risk that could be associated with different clinical use contemplated for Gynemesh PS versus the Prolene Soft Mesh. Thus, since there were no differences that related to any of the categories cited by Dr. Dunn, Ethicon's completion of the form was appropriate.

7. Ethicon Properly Staffed Its Risk Analysis Teams

Dr. Dunn opined that Ethicon failed to properly staff some of its design FMEA teams. I disagree. Ethicon included the appropriate expertise on its teams.[75]

8. Dr. Dunn's Opinion that Ethicon Knew about Oxidative Degradation is Correct, But His Opinion That Ethicon Failed to Consider Oxidative Degradation Is Wrong

Dr. Dunn discusses internal Ethicon studies and emphasizes that Ethicon knew about oxidative degradation as early as the 1980s. However, Dr. Dunn either did not know about, or ignored, what appears to be an exhaustive analysis of polypropylene as a medical implant, including the effects of oxidative degradation.[76] Ethicon certainly knew about oxidative degradation of polypropylene, which was discussed in the public document "Reclassification of Nonabsorbable Polypropylene Surgical Suture from June 5, 1990, published by the US FDA.[77] On page 7 of the determination to down-classify nonabsorbable sutures from Class III to Class II, FDA discussed the loss of tensile strength leading to suture breakage and that retention of the suture's tensile strength is critical to the function of the suture. FDA's report recognizes that the "loss of tensile strength in vivo is primarily related to the oxidative degradation of the polypropylene polymer and that the polymer's degradation proceeds slowly and is generally not considered clinically significant under normal circumstances." FDA also declares in the same report "that the cumulative risk of nonabsorbable polypropylene surgical suture breakage is small, and its ability to function properly is uncontested." Dr. Dunn simply cannot credibly speak of Ethicon's knowledge without acknowledging the importance of Ethicon's knowledge of these independent research-based findings.

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[75] See, e.g., ETH.MESH.01412964.XLS; ETH.MESH.07254733-ETH.MESH.07254735.
[76] ETH.MESH.06934664-ETH.MESH.06934688.
[77] *Id.*

Dr. Dunn says that Ethicon's dFMEA for Prosima did not consider oxidative degradation. However, the dFMEA on which he relies expressly states that an earlier DDSA must be reviewed for analysis of the Prolene Soft Mesh properties.[78] This DDSA and earlier DDSAs that I have cited above expressly considered whether biodegradation was a hazard of Prolene Soft Mesh. The DDSAs correctly state that the consideration must comply with EN 30993, or ISO 10993. ISO 10993 expressly includes oxidative degradation as one of the forms of biodegradation. Ethicon correctly concluded that the extensive history of safe clinical use of Prolene and Prolene meshes demonstrated that biodegradation, which includes oxidative degradation, is not a concern from a clinical standpoint.

Dr. Dunn opines that Ethicon ignored its own internal studies that include discussion of oxidative degradation that he claims should give rise to concerns. However, Dr. Dunn ignored the fact that the findings in Ethicon's internal studies were totally consistent with the FDA's findings concerning oxidative degradation.

Moreover, Dr. Dunn's attributions to these studies are inaccurate and biased as shown in the following chart:

Dr. Dunn's summary	**What the reports say that he didn't mention**
In 1982, Dr. Anthony Lunn reported in an internal Ethicon study that surface cracks were found on Prolene sutures explanted from vascular implants and ophthalmic implants. Specifically, this report evaluated the surface crack depth on these implants. Surface cracks were found on sutures from both the vascular and ophthalmic implants. Dr. Lunn pointed out that "crack depth does not vary systematically with implantation time; it does vary from point to pint [sic] along the fiber length.	Dr. Dunn failed to mention that one of the tables of specimen to which Dr. Dunn refers lists many specimen with no cracking observed, some as old as 6 years and some specimen with no dates included.[79]
In 1983, Ms. Barbara Matlaga and Drs. W. D. Sheffield and A. W. Fetter published in an internal Ethicon study on Prolene (polypropylene) microcracks. In this report, the authors noted that the "latest "[sic]human retrieval" specimens of Prolene suture showed surface microcracking. They further reported that they could show slides of these cracks "at the next Prolene Microcrack Committee" meeting. Furthermore, they concluded "surface cracking was noted on the Prolene sample from both	Dr. Dunn failed to mention one of the most important observations made in the report from the standpoint of a risk analysis concerning degradation: "the reaction around the Prolene suture was minimal in all cases."[80] Dr. Dunn failed to mention the numerous specimen in this collection of reports that did not show microcracking, including specimen that were 3-5 years old, 2.5 years old and 7.5 years old.

[78] ETH.MESH.01412964.XLS.
[79] ETH.MESH.15406978.
[80] ETH.MESH.15955438-ETH.MESH.15955473.

Dr. Dunn's summary	**What the reports say that he didn't mention**
explants. Why the cracking occurred or it [sic] this condition contributed to the loss of breaking strength (54%) could not be determined from this type examination".	Dr. Dunn failed to mention that one of the reports in this collection stated that no cracks were present until the explants were dried. The specimen that was tested at 54% remaining tensile strength had been observed to have had instrument damage so the tested portion was from a segment of this specimen which had "relatively little" damage. Since Dr. Dunn was focused on tensile strength, it is significant that he failed to mention that the reports show that for size 4-0 Prolene, the average remaining tensile strength for sutures explanted after up to 7 years was still 98.25%. Clearly, the sutures retained ample strength for far more than enough time for a Prolene mesh to perform its job as a bridge for building tissue. These studies show how diligently Ethicon scientists as early as 1983 were studying the effects of time in-vivo on surface morphology. They also support the conclusion of risk analysts that no further degradation studies are needed.
In 1984, Dr. Peter Moy reported in an internal Ethicon study that microcracking of explanted Prolene sutures from vascular grafts was observed. Dr. Moy points out that "a great body of literature exists regarding oxidative degradation of polypropylene in general as well as selective studies on the photo- and thermal-oxidation of polypropylene monofilaments". He recommended further studies to examine "known oxidized Prolene samples".	Dr. Dunn failed to mention the observation that "the thermal characteristics of the crack layer on explants suggests as an alternative that the layering effect may be due to a biological deposit. The characteristics of a proteinaceous layer on Prolene suture was considered by immersion of virgin fibers in human serum and air dried. Figures 10-12 show serially the same temperature sequence as shown for the explants. We see that the protein layer has similar characteristics to the crack layer on explants in that it separates from the fiber cleanly with heating and maintains its form after the Prolene fiber has melted. Further, the superficial resemblance of such a serum coated fiber to a "young" explant (1 year) is strong (compare Figure 13-14). The epitaxial nature of the coating is good enough in fact to

Dr. Dunn's summary	**What the reports say that he didn't mention**
	show the extrusion lines of the underlying fiber surface, Figure 15."[81]
In 1985, a new Ethicon internal study was initiated where "twenty-four Beagle dogs were implanted in November 1985 with sutures made from four different polymers. Each polymer suture type was implanted in six different locations (sites) in each dog. One of the suture polymer materials included in this study was Prolene sutures. The study was referred to in Ethicon internal memos as the "In Vivo suture study".	Dr. Dunn failed to mention that the explanted sutures from dogs 1994, 2000 and 2006 did not show any cracking or abrasions. On explants from dogs 2012 and 2018 a few cracked areas were observed; both of these sutures came from site 4.[82]
In 1987, Daniel F. Burkley, a Principal Scientist at Ethicon, examined Prolene sutures that were "carefully removed from human vascular graft explants". Sutures were examined that had been in the body for 2 years and 8 years, respectively. Mr. Burkley conducted chemical analysis using infrared spectroscopy and also performed microscopic examination. Sutures that were in the body for eight years "were severely cracked specimens". Furthermore, Mr. Burkley stated that the surface of the sutures appears to be degraded polypropylene. He further concludes that he observes no protein in the FTIR (Fourier Transform Infrared Spectroscopy) spectra of the explanted sutures and that the FTIR spectra show that scraped surface material is consistent with polypropylene that has been "degraded in an oxidative fashion". He also observed changes in the DLTDP concentration, one of the antioxidants in Prolene, in the explanted Prolene sutures. He specifically reports that there is "no DLTDP observed in the surface scraped (cracked regions)" and that "the observed DLTDP decreases with implant time". Finally, Mr. Burkley also reported that the surface scrapings from the sutures that had been in the body for eight years (severely cracked) showed a melting	Dr. Dunn failed to mention that the degraded portion of the 8-year explant makes up only a minor portion of the entire suture.[83]

[81] ETH.MESH.15958452-ETH.MESH.15958469.
[82] ETH.MESH.11336474-ETH.MESH.11336487.
[83] ETH.MESH.12831391-ETH.MESH.12831404.

Dr. Dunn's summary	**What the reports say that he didn't mention**
point between 147-156°C and that "this is the melting range previously observed for oxidatively degraded polypropylene."	
In 1990, Elke Lindemann wrote an internal Ethicon five year report on the "In Vivo suture study". Specifically, five of the dogs were euthanized and the suture implants were removed for scanning electron microscopy examination. She concluded "out of seven Prolene explants, two revealed cracking". She further concluded that "after 5 years in vivo the PVDF suture was the only explanted material from five dogs that did not show any surface damage due to degradation." This is consistent with the potential for oxidative degradation previously shown in Figure 2 of this report.	This is the exact same report that Dr. Dunn cited above. He is duplicating the same citation and referring to the document in a different way, quoting different parts of the same study.
In 1990, Elke Lindemann, Eugene Muse, and Daniel Burkley, wrote an internal Ethicon seven year report on the "In Vivo suture study". Specifically, four of the dogs were euthanized and the suture implants were removed for scanning electron microscopy examination. These Ethicon scientists concluded in this report that "the 7 year in vivo results generally substantiated the five year findings". The group further concluded that "degradation in Prolene is still increasing and PVDF, even though a few cracks were found, is still by far the most surface resistant in-house made suture in terms of cracking". Again, this is consistent with the potential for oxidative degradation previously shown in Figure 2 of this report.	Dr. Dunn didn't quote portions of the report that did not fit his theory:[84] "Gel Permeation Chromatography (GPC) was run on Prolene sutures explanted from dogs after seven years. The GPC data was compared to data from a current 4/0 Prolene suture. The results indicate that there was no significant difference in molecular weight between the 4/0 Prolene control and the seven year explants." Moreover, he completely ignored the lab findings of "no degradation" or "no significant degradation" or "no molecular weight degradation." NOTE: if significant changes in molecular weight were found there might have been concern for physical property changes, but this was not the case.

[84] ETH.MESH.09888187-ETH.MESH.09888223.

Thus we can see that Dr. Dunn has presented only statements from these internal reports which fit his theory and ignored everything stated that contradicted his theory. He has stated that the engineers should have known to be concerned because of these internal reports, but these reports do not suggest any form of physical or chemical "failure" of the sutures. Dr. Dunn wishes us to believe that surface level oxidation (in-vivo), is a CAUSE of clinical device failure, but he has not produced evidence of this occurrence in clinical literature. Moreover, he has not established an observed harm from his hypothesis of failure. Dr. Dunn simply cannot show a relationship between surface oxidation in-vivo and any observed clinical FAILURE or HARM.

Dr. Dunn seeks to establish that observations of "microcracking" of explanted Prolene is a cause for mesh "failure". At the time of Ethicon's various risk analyses, and even today, complaints for device performance in the clinical application have not been linked to a "root cause" of microcracking due to surface oxidation.

The strength of a construct, such as a mesh, is very dependent upon the mechanical properties of both the fiber AND the construction technique. It is also valid for a biomedical engineer to ascertain how the construct (mesh or web) differs from the construct of a single suture. What differs in biomedical engineering from say, civil engineering, is the mesh is designed to become incorporated by tissues, and the fibrous tissue typically creates a composite structure stronger than the original man-made material. This new composite structure can be formed in a matter of weeks but certainly months, unless there is infection present. Any biologic process that would inhibit in-growth to form this composite structure would be a root cause of the mesh failure to perform its intended function. If the mesh were to become infected the failure MODE could be failure to incorporate and the EFFECT could be the necessity of explanting the mesh if antibiotic treatment failed. Such medical intervention is considered severe. This is exactly why the Ethicon engineers focused much of their analysis of FAILURE MODES and EFFECTS ANALYSIS on the many potential causes of infection. The cause of infection is known to be attributable to poor surgical technique (which could contaminate the sterile product), the potential break of the sterile packaging barrier, and insufficient sterilization methods. It was their task to mitigate these risks to infection, and in fact one of the stated goals of the "MINT" project was to develop a surgical system that would help to improve the technique, and thereby reduce that potential risk for infection.

Dr. Dunn's focus on microcracking is simply another instance of his looking for a "cause" where no HARM has been identified.

9. Dr. Dunn's Opinion that Ethicon's External Consultants "Reported that Oxidative Degradation Was a Likely Cause of Polymer Failure in Its Mesh Devices" Is a Gross Misrepresentation of the Content of the Report

Dr. Dunn opined that Ethicon's external consultants "reported that oxidative degradation was a likely cause of polymer failure in its mesh devices." I disagree. Oxidative degradation was not the focus of the report to which Dr. Dunn refers, but rather the report concerned an investigation into potential causes of mesh exposure, a known but low risk of Prolene Mesh products that Ethicon has carefully reviewed for years. I do agree with Dr. Dunn's implicit opinion that it was appropriate for Ethicon to engage an external consultant to assist in yet another review of mesh erosions. I also agree with Dr. Dunn's implicit opinion that it would be appropriate for Ethicon's

risk management team to consider such a report on a review of literature and physician consultation. Industry standards expect risk management teams to engage such reviews. Dr. Dunn gives the improper impression that the report findings concerned Ethicon's Prolene Mesh. The only discussion of oxidative degradation appears on page 35. In fact, the consultants were reviewing literature and thus the citations concern polypropylene in general (such as "where sutures were used to implant an intraocular lens"). This is made clear by the observation that anti-oxidant additives make polypropylene more resistant to oxidation. The Executive Summary does not even mention degradation and nowhere does the report even remotely suggest that oxidative degradation has caused Prolene Meshes to "fail" in any respect. The report declined to make any finding regarding a cause of mesh erosion. The report does not contain any new information concerning oxidative degradation that had not already been considered by both the FDA in its 1990 study and by Ethicon in its prior studies.

10. Dr. Dunn's Opinions Concerning Long Term Storage Lack Any Basis

Dr. Dunn opined that:

- *Long-term storage of the raw material used to create these meshes prior to extruding the monofilament fibers poses substantial oxidation concerns.*

- *As a supplier of permanently implantable medical devices, by failing to control its resin and processing of these meshes with respect to polypropylene's inherent tendency to oxidize, Ethicon has failed to account for the risk associated with its degradation for all those who buy, implant or are implanted with these products.*

However, Dr. Dunn failed to provide any reference or analysis for these opinions. Dr. Dunn does not appear to have made consideration of the records demonstrating qualification of material suppliers, raw material specifications, controls on the extrusion process and knitting procedures, and FIFO control systems at the facilities. Such controls are part of the quality system procedures he failed to explore. Quality system procedures mitigate risks associated with quality of the resin, processing of the resin into mesh, and potential effects from manufacturing and storage. Furthermore, these quality systems procedures and their effectiveness are monitored by the auditors from numerous regulatory authorities.

In my opinion Dr. Dunn has attempted to raise concerns and make baseless allegations about material storage conditions without offering anything more than innuendo.

FACTS OR DATA CONSIDERED IN OPINION

The facts and data that I have considered in arriving at my opinions are referenced above throughout my report. Additional materials that I have considered are also listed in Exhibit A.

EXHIBITS

I have not yet determined what exhibits I may use at trial to explain my opinions. I will do so in accordance with the instructions I receive from the court and counsel.

COMPENSATION

The rates at which I am being compensated are as follows:

- $250 per hour for time spent not involving travel;
- $325 per hour for time spent including travel, deposition, or trial testimony.

CASES IN WHICH TESTIMONY HAS BEEN GIVEN

In Re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, Master File No. 2:12-MD-MDL 2327 in the United States District Court for the Southern District of West Virginia, Joseph R. Goodwin, U.S. District Judge - - Deposition taken in Mullins, et al. v. Ethicon, Inc., No. 2:12-cv-02952, et al, on October 6,2015.

RESERVATION OF RIGHTS AND SIGNATURE

The fact that I do not explicitly mention all of Dr. Dunn's statements should not be understood as an agreement with his statements. Moreover, my opinions are expressed to a reasonable degree of professional certainty within my field of expertise. I have reviewed voluminous documents but reserve my right to evaluate additional documents in the future and revise or supplement my opinions as necessary thereafter.

Elaine Duncan

Digitally signed by Elaine Duncan
DN: cn=Elaine Duncan, o=Paladin Medical, Inc., ou=President, email=duncan@paladinmedical.com, c=US
Date: 2016.03.01 10:09:59 -06'00'

Elaine Duncan, M.S., M.E., RAC
President of Paladin Medical, Inc.
Date: February 29, 2016